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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MINNIFIELD, NITA M	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/613,916	KRIEG ET AL.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-112* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 4 pg

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 7-03-03, 12-15-03, 1-28-04 total 8 pg

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 24,31,34,38,45,47,55,62,65,69,76,78,85,88,91,93,95,101,104,109 and 111.

Continuation of Disposition of Claims: Claims rejected are 19-23,25-30,32,33,35-37,39-44,46,48-54,56-61,63,64,66-68,70-75,77,79-84,86,87,89,90,92,94,96-100,102,103,105-108,110 and 112.

DETAILED ACTION

1. Applicant's election with traverse of Group I, species election Mycobacterium *M. tuberculosis* and sequence GTCGTT in the reply filed on May 26, 2006 is acknowledged. The traversal is on the ground(s) that a search of Group II would likely be coextensive with a search of Group I and therefore would impose no significant additional burden of searching upon the Examiner. Upon further review of all of the claims and Applicants' comments, Groups I and II have been rejoined. However, the species requirement is maintained. In view of combining Groups I and II and the species requirement (Mycobacterium *M. tuberculosis* and sequence GTCGTT), claims 19-23, 25-30, 32, 33, 35-37, 39-44, 46, 48-54, 56-61, 63, 64, 66-68, 70-75, 77, 79-84, 86, 87, 89, 90, 92, 94, 96-100, 102, 103, 105-108, 110 and 112 will be examined in the instant application. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24, 31, 34, 38, 45, 47, 55, 61, 65, 69, 76, 78, 85, 88, 91, 93, 95, 101, 104, 109 and 111 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 26, 2006.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 19-23, 25-30, 32, 33, 35-37, 39-44, 46, 48-54, 56-61, 63, 64, 66-68, 70-75, 77, 79-84, 86, 87, 89, 90, 92, 94, 96-100, 102, 103, 105-108, 110 and 112 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for treating a mycobacterium infection (tuberculosis) in a subject, the method comprising: administering to a subject an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide (i.e. see various formulas in claims 26-29 for example, GTCGTT), in an amount effective to treat, prevent or ameliorate an infection with a Mycobacterium bacterium (for example *M. tuberculosis*), thereby treating the infection (mycobacterium) in the subject.

The specification does not teach any of the methods as set forth in the instant claims for treating, preventing or ameliorating mycobacterium infections in a subject. The specification teaches numerous in vitro experiments, however these data do not indicate enablement for the claimed invention. The specification does not teach that any of the myriad of possibilities of CpG immunostimulatory nucleic acid molecule having the claimed formulas can be used to treat, prevent or ameliorate mycobacterium infection and specifically infection caused by *M. tuberculosis* in a subject.

The state of the art with regard to CpG and treating, preventing or ameliorating mycobacterium infection and specifically infection caused by *M. tuberculosis* in a subject is unpredictable.

The history of vaccination in humans (the scope of the instant claims) against Mycobacterium disease (tuberculosis) is notorious for lack of a successful protection (i.e. prevention) as well as amelioration. At the time of filing, there still remained a lack of correlation of success in animal models with successful vaccination of humans against mycobacterial disease, as evidenced by (Wiegeshaus, E.H. et al, Reviews of Infectious Diseases, April 1989, 11/Suppl. 2:S484-S490). Animal models used to evaluate the relative protective potency of a panel of tuberculosis vaccines have yielded dissimilar data (abstract). Wiegeshaus et al teaches that animal models have produced disparate data on the protective potency of tuberculosis vaccines, therefore the variables comprising such models cannot be randomly chosen and that it is not known which animal model, if any, predicts the protective potency of vaccines for humans (page S490). Griffin et al (Trends in Microbiology, Nov. 1995, 3/11: 418-424) teaches that limitations in the design of field studies have seriously compromised our ability to evaluate the efficacy of bacilli Calmette-Guerin (BCG) in human and animal populations accurately. Griffin et al teaches that humans, cattle, deer, guinea pigs and rabbits have similar pathology but differ in their susceptibility to tuberculosis (p. 418). Griffin et al teaches that although studies in guinea pigs and rabbits have made an important contribution to our understanding of virulence and pathogenesis of tuberculosis they have limited use for the study of the protective immune response (page 418-419). Griffin et al teaches that multiple factors influence the development of protective immunity to mycobacterium are complex and difficult to characterize and considering the variables the influence experimental infection and protective immunity it is essential to develop standardized animal models and test systems to define the immune parameters in vivo and in vitro that protect

against virulent mycobacterium. Griffin et al teach that the lack of agreement about the efficacy of BCG seen after 60 years of its widespread use in more that 3 billion humans and the variable results from extensive laboratory animal studies suggest that further empirical studies are unlikely to help in assessing the efficacy of new generation vaccines against tuberculosis. Griffith et al teaches that it is essential to exploit the theoretical knowledge obtained from laboratory studies and to develop definitive in vitro markers of protective immunity in parallel with infection studies that evaluate functional protection in vivo (page 419). Griffin et al further teach that many critical factors that are required to generate protective immunity and target the cellular pathways for appropriate T cell activation and effector activity against tuberculosis have been identified and the ability to exploit this knowledge depends on relevant animal models being available to test new candidate vaccines (pages 422-423).

The prior art has shown that limitations in the design of field studies have seriously compromised our ability to evaluate the efficacy of Mycobacterium vaccines in human and animal populations accurately, they differ in their susceptibility to tuberculosis and animals models have limited use for the study of the protective immune response. The prior art has also shown that multiple factors that influence the development of protective immunity to mycobacterium are complex and difficult to characterize. The prior art has taught that there are many variables that influence experimental infection and protective immunity and that it is essential to develop standardized animal models and test systems to define the immune parameters in vivo and in vitro that protect against virulent mycobacterium. The prior art has also shown the limitations of using guinea pigs or mouse models to evaluate protective immunity.

The state of the art is unpredictable with regard to treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms (See Krieg et al, Weiner and McCluskie et al for recent advances using CpG oligonucleotides). Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (See McCluskie et al in its entirety, and especially on page 296; see Krieg et al on page 524). Weiner states furthermore that the molecular mechanisms of CpG oligonucleotides' immuno-stimulatory effects are not yet understood (See especially page 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (See Agrawal et al especially on pages 78-80). Further, Weiner cautions that despite therapeutic promise of some CpG ODNs, all CpG ODNs are not alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset or CpG ODN sequence. Weiner teaches that the clinical effects of CpG ODN have not yet been explored and further work with the immunostimulatory nucleic acids in both the laboratory and the clinic are needed before their true promise as investigational immunological and therapeutic agents is known.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. The skilled artisan would not reasonably expect success in using animal models to assess protective immunity against Mycobacterium infections in humans

because they differ in their susceptibility to Mycobacterium infections, in particular tuberculosis nor would the skilled artisan expect success using an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide to treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject. The skilled artisan cannot conclude from the absence of data in the specification and the state of the prior art that an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide can treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject because the prior art regarding the use of animal models in assessing protective immunity for Mycobacterium infections (tuberculosis) is unpredictable and not well established. The specification is devoid of data to support that the claimed method can successfully to treat, prevent or ameliorate mycobacterium infection (tuberculosis) in a subject using an immunostimulatory nucleic acid molecule comprising an unmethylated CpG dinucleotide. There are no animal models. This demonstration is necessary to enable the claimed methods. It is noted that the claims only indicate that the CpG is administered. The state of the art with regard to such a method is unpredictable, as well. O'Hagan et al 2001 does teach that the CpG has adjuvant properties and that this effect appears to be maximized by their conjugation to protein antigens or their formulation with delivery systems (p. 75). There is no evidence of record or in the state of the art that indicates that CpG administered alone will be successful in the treatment, prevention or amelioration of Mycobacterium infections (tuberculosis) in a subject, human or otherwise. O'Hagan et al teaches that "[A]lthough, it is too early to know in which situations CpG oligo's might prove to be most advantageous, their apparent ability to selectively manipulate Th1 responses is most exciting. Nevertheless, the safety of

CpG DNA needs to be firmly established in the clinic, since the induction of autoimmunity with CpG immunization can be shown in various established animals models (citation omitted). However, the relevance of these observations to human studies is unknown." (p. 75)

There are no working examples in the instant specification that show the claimed methods can treat, prevent or ameliorate Mycobacterium infection (tuberculosis) in a subject. The skilled artisan cannot conclude that a protective immune response can be achieved using any host with the information provided in the specification and an undue amount of experimentation would be necessary to practice the claimed invention by using the limited information disclosed in the specification. Therefore, the specification fails to enable the claimed invention.

The state of the art post-filing as well as the specification indicates that the scope and breath of the claimed invention is not enabled. The claims contemplate a myriad of possible oligonucleotides having the CpG motif and range in size from 8 to 100 nucleotides (see claims 26-29 for example) and unlimited nucleotides (see claim 19 for example). The specification has not shown that the myriad oligonucleotides contemplated by the claims will function in a method that treats, prevents or ameliorates mycobacterium infections (tuberculosis) in a subject.

It is noted that the specification describes the steps of the claimed method to one skilled in the art, but does not provide any evidence that any of the claimed methods would function *in vivo* or *in vitro*. The issue of correlation is related to the issue of the presence or absence of working examples. Correlation as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a working example, if that

example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute working examples. (see MPEP 2164.02) The pending specification does not set forth such correlations for a working example of the claimed *in vivo* method.

The claimed invention must be enabled as of the filing date of the patent application, not enabled by publications post filing. Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each

application based on its filing date. 35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used. (see MPEP 2164.05(a))

The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated

application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled.

Further, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). Although, typically,

inoperative embodiments are excluded by language in a claim (e.g., preamble), the scope of the claim may still not be enabled where undue experimentation is involved in determining those embodiments that are operable. A disclosure of a large number of operable embodiments and the identification of a single inoperative embodiment did not render a claim broader than the enabled scope because undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976). However, claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the claimed invention without undue experimentation. In *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated: Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of

record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification using the claimed methods to treat Mycobacterium infections (tuberculosis) in subject administering a CpG immunostimulatory nucleic acid molecule as previously stated, 3) there are no working examples presented in the specification that teach the claimed methods to treat, prevent or ameliorate Mycobacterium infections as previously stated, 4) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level), and 5) the state of the art in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, it is determined that it would require undue experimentation to practice the claimed methods.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 22, 36, 49, 53, 67 and 80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 22 and 53 are vague and indefinite in the recitation of "sufficient immunostimulatory motifs to be immunostimulatory". What is the minimum number of CpG motifs needed to be deemed sufficient to be immunostimulatory? Claims 36, 49, 67 and 80 are vague and indefinite in the recitation of "immune system is not functioning in a normal capacity". What does Applicant intend by "normal capacity" with regard to an immune system; what are the metes and bounds of normal?

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

9. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or Form PTO-1449 have been previously cited and made of record in related applications 09/818918, 09/337584, 09/337893 as well as others.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Minnifield
Primary Examiner
Art Unit 1645

NMM
August 7, 2006